Journal Lancet
Lancet Publications
Northwestern Pediatric Society
25th South 10th Street
Minneapolis 3, Minnesota

VOLUME XII February 1956 NUMBER 2

UNIVERSITY OF MINNESOTA
AUG 8 1957
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Clinical Proceedings

OF THE

CHILDREN'S HOSPITAL

WASHINGTON, D. C.

BILIARY ATRESIA WITH CHOLEDOCHAL CYST. *Neville K. Connolly, M.D., Grace H. Guin, M.D., Joseph M. LoPresti, M.D., J. William Oberman, M.D.* 19

HEREDITARY DEFECTS OCCURRING IN A RACIAL ISOLATE RESIDING IN SOUTHERN MARYLAND. *Carl J. Witkop, Jr., D.D.S., Hazel R. Dyson, R.N., Lee M. Sackett, D.D.S.* 29

TETRALOGY OF FALLOT. *George William Ware, M.D.* 34

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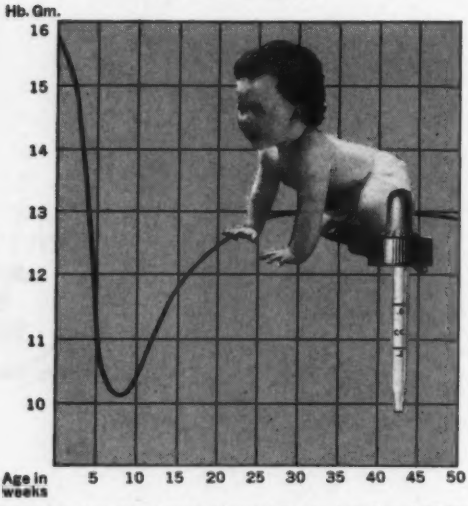

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(1) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86: 553, 1954. (2) Smith, C. H.: Bull. New York Acad. Med. 30: 155, 1954. (3) Smith, N. J., and Roselle, S.: J. Clin. Nutrition 1: 275, 1953. (4) Sturgeon, P.: Pediatrics 13: 107, 1954.

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Cases are selected from the weekly conferences held each Sunday morning at 11:00 A.M., from the Clinico-pathological conferences and from the monthly Staff meeting.

This bulletin is printed for the benefit of the present and former members of the Attending and Resident Staffs, and the clinical clerks of Georgetown and George Washington Universities.

Subscription rate is $2.00 per year. Those interested make checks payable to "Clinical Proceedings Dept.," The Children's Hospital, Washington, D.C. Please notify on change of address.

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Entered as second class matter November 21, 1946 at the post office at Washington, D.C., under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 538, Act of February 28, 1925, authorized January 17, 1947.

BILIARY ATRESIA WITH CHOLEDOCHAL CYST OR PSEUDOCYST

SUNDAY CONFERENCE CASE

Neville K. Connolly, M.D.
Grace H. Guin, M.D.
Joseph M. LoPresti, M.D.
J. William Oberman, M.D.

In this case, obstructive jaundice in the neonatal period prompted surgical exploration of the biliary system on two occasions, and later surgery for relief of intestinal obstruction. The common bile duct apparently had no lumen. At autopsy, biliary cirrhosis of the liver and a choledochal cyst or pseudocyst were present. This case is presented because it exemplifies the problem of jaundice in the newborn and because such a combination of findings is unusual.

CLINICAL SUMMARY

This 1 year old colored girl was born at another hospital on September 7, 1954, weighing 2.3 kilograms, and showing a generalized jaundice. She was the product of an 8 months pregnancy complicated by sub-acute toxemia. On the second day of life, treatment for sepsis and bladder infection was started; the baby was placed on artificial feeding, and was discharged at 13 days of age with persistent jaundice. At 3 months of age, on December 15, 1954, severe abdominal pain occurred and there was a generalized convulsion. She was then readmitted to the hospital of her birth where surgical exploration established a diagnosis of biliary atresia. The distal portion of the common duct was atretic; the gall bladder and the cystic duct were rudimentary; but there was a return of bile on aspirating the common duct which was too small to be intubated by a "T" tube. A polyethylene tube was inserted in the common duct and drained through a stab wound. No bile return from this tube was ever recorded. On March 9, 1955, the baby was transferred to an outlying hospital, and in the process of transfer, the polyethylene tube was dislodged and lost. The biliary fistula sealed rapidly and subsequent clinical and laboratory data indicated obstructive jaundice and increasing hepatic damage. Surgical exploration was again contemplated but deferred because of lack of a "T" tube sufficiently small. The baby was discharged on May 20. She had frequent bouts of vomiting and diarrhea, clay-colored stools, and chronic upper respiratory infection. Meanwhile, her abdomen became progressively larger. On September 9, she became irritable and started to cry continuously. After 3 days, the patient was seen in the Out Patient Department of Children's Hospital and was admitted for investigation and treatment.

On admission physical examination she was a poorly developed and nourished colored girl in no distress, weighing 6.8 kilograms. The abdomen was prominent; there was generalized jaundice; the sclerae and oral mucosa were markedly icteric. The liver was palpable 2 cm. below the right costal margin; 3 cm. below this was a linear scar 11 cm. in length. Below were two other scars 0.5 cm. each. The remainder of the physical examination was normal.

On admission the following hemogram was obtained: Hemoglobin 8.7 gms. per 100 ml., leukocytes 12,000 per cu. mm., with segmented forms 51 per cent, lymphocytes 41 per cent, monocytes 4 per cent, eosinophils 4 per cent, and adequate platelets. Sickle cell preparation was negative. The urine was clear yellow with a 4 plus bilirubin test. Tests for the bilirubin and urobilin in the stool were negative. The direct bilirubin in the serum was 3.28 mgm. per 100 ml., and the total bilirubin was 5.20 mgm. per 100 ml. The total protein was 8.4 gms. per 100 ml; the A/G ratio was 1.3/1 and thymol turbidity, 12.1 units. The VDRL was reported negative. On September 12, the cephalin flocculation test was reported negative in 48 hours. The prothrombin time on September 13, was 42 per cent of normal activity, and 21 per cent on the next day. Six hours after intravenous injection of vitamin K, the prothrombin time corrected to 95 per cent of normal. The serum cholesterol was 512 mgm. per 100 ml., and the cholesterol esters 230 mgm. per 100 ml. X-ray examination of the abdomen on September 16 was suggestive of some enlargement of the liver, but otherwise was negative.

On September 21, an exploratory laparotomy was performed; the liver was dark green, quite large and finely nodular. The gall bladder was found to be collapsed, measuring 2 cm. in length and 0.5 to 0.8 cm. in diameter. The duct structures were traced, the cystic duct averaging 0.1 to 0.2 mm. in diameter. The common duct was dissected and appeared to be a firm fibrous structure. Needle aspiration of the lumen of the ducts was unsuccessful. The cystic duct was transected and no bile escaped from either end. The common duct was then divided close to the duodenum and transected in short sections and no lumen could be found. Attempt to establish a connection between the biliary and intestinal tracts was abandoned.

The post-operative course was marked by persistent vomiting, progressive abdominal distension with oozing of yellowish fluid through the surgical wound and gradual cessation of the peristaltic sounds. A barium enema on September 27 confirmed the diagnosis of intestinal obstruction.

On September 28, a surgical exploration was performed through the previous incision. The small bowel was found to be dilated and the site of obstruction was localized in the terminal ileum about 10 cms. proximal to the ileocecal valve. This terminal segment of the ileum was also adherent to the under surface of the liver. As the obstructed bowel was being freed from the liver, the proximal dilated segment of the ileum ruptured spontaneously and 350 to 400 ml. of clear fluid were aspirated from the lumen of the bowel which was then repaired.

The post-operative course was uneventful. On October 2, oral feedings were resumed and the baby passed a clay colored stool on the following day. The general condition of the baby remained poor and she died on October 21, 1955, on the forty-second day of hospitalization at 13 months of age.

DISCUSSION

Autopsy Findings

Dr. Guin:

On opening the abdomen at autopsy a thick walled, shaggy, dark green cyst was found; this contained 500 cc. of dark green, thin, creamy material and measured 8.0 cm. in diameter. It was adherent to the posterior surface of the right lobe of the liver and was attached firmly to the omentum. The gall bladder, cystic, and common ducts were absent.

Inside the cyst on its inferior surface was a 1.0 mm. depression. In the superior portion two probe-patent openings which communicated with the liver were encountered. These were interpreted as being the right and left hepatic ducts. On microscopic examination, smooth muscle cells were scarce and replaced by collagen strands and fibrous tissue. An acute inflammatory reaction was observed. No mucosal surface could be identified.

The liver on gross and microscopic examination disclosed the classical picture of biliary cirrhosis. The cut surface was finely nodular and dark green. Thick bands of fibrous tissue extended from the triads, separating groups of hepatic cells into a reticulated pattern. The bile canaliculi were plugged and distended with bile. Bile duct proliferation was present, but the majority of these newly formed structures were empty.

Final diagnosis was either congenital choledochal cyst or pseudocyst with biliary cirrhosis.

There was a report in *Clinical Proceedings* in 1947, which reviewed all of the cases of congenital duct abnormalities, and at that time (from 1943 to 1947) there were 13 cases at this hospital. I do not believe such a review has been made since then, but I believe we have again, almost as many cases. In that group of 13, 7 were found to be operable, but only 2 survived. One of the cases that did not survive was a choledochal cyst such as this but not exactly like it. The one that we had in 1946 revealed right and left hepatic ducts, intact gall bladder and cystic duct but dilatation of the common duct.

Dr. LoPresti:

Jaundice in the early weeks of life is a relatively common problem and represents one of the most interesting clinical situations with which the pediatrician is faced. Initially it is important for him to determine whether the jaundice is retentive or regurgitative; then, if it appears that a regurgitative type of jaundice is present, he must decide whether the regurgitation of bilirubin into the blood stream is the result of parenchymal liver damage or is due to a congenital or other type of obstruction in the biliary drainage tract. Regurgitative jaundice secondary to hepatocellular damage, of course, is an inoperable situation, whereas most of the true biliary obstructions require some form of surgical exploration. One can gain a very good idea of what is going on in the jaundiced infant by performing a few simple laboratory procedures. I must stress, however, that the interpretation of the laboratory results must be correlated with the clinical findings. The tests which should be performed in the presence of jaundice, the etiology of which is not clinically apparent, are the examination of blood for total bilirubin, the urine for bilirubin and urobilino-

gen, and the stool for urobilinogen. If these tests are performed carefully and correctly, one can decide whether he is dealing with a retentive or regurgitative jaundice, and whether the regurgitative jaundice is hepatocellular or obstructive.

Often, it will not be possible to differentiate hepatocellular jaundice in the obstructive phase from the jaundice of true biliary atresia. In both conditions, at any given time, the stools may be acholic. One, then, must utilize liver function tests. However, liver function tests must be interpreted rather loosely. No one liver function test will tell you exactly with what condition you are dealing. In addition, even in the presence of extensive liver damage, liver function tests may be normal. In general, however, liver function tests will be abnormal in the presence of parenchymatous liver damage. When the liver function tests are abnormal in a patient who has regurgitative jaundice, one may assume that he is dealing with hepatocellular jaundice and that surgical exploration in such a patient is probably contraindicated. I would like to say a word about one test of liver function which is often neglected and not used as widely as I believe it should be. This is the prothrombin time. The prothrombin time may be prolonged because the liver is not forming prothrombin (hepatocellular damage), or it may be prolonged because there is no bile reaching the duodenum to aid in absorption of vitamin K. All one need do in the presence of a prolonged prothrombin time in a patient who has a regurgitative jaundice is to administer a parenteral injection of vitamin K and recheck the prothrombin time in a suitable interval. If the prothrombin time returns toward normal, it is obvious that the patient does not have severe liver cell damage, and that the jaundice is probably due to an obstruction. On the other hand, if the prothrombin level is not appreciably affected by the administration of vitamin K, one can assume that there is a good deal of liver cell damage present. Since a low prothrombin time may give rise to bleeding tendencies, vitamin K injection has therapeutic value as well.

Most cases of true obstructive jaundice require surgical exploration with the expectation of relieving the obstruction. The one exception is obstructive jaundice due to inspissated bile. I might caution first of all that the inspissated bile syndrome is usually associated with excessive hemolysis and most frequently accompanies hemolytic disease of the newborn, the Rh or ABO incompatibilities. It may not be possible to differentiate the two and only observation of the patient over a period of time will result in a correct answer. In most of the patients with inspissated bile, the biliary radicals will unplug eventually and the jaundice will be alleviated. Occasionally, however, the only way to differentiate inspissated bile from true biliary atresia is surgical exploration.

In conclusion, it has become more and more apparent that regurgitative jaundice even in the newborn period may be the result of viral hepatitis.

Frequently, one will be unable to differentiate viral hepatitis in the newborn from a surgical obstructive jaundice.

Dr. Connolly:

This is a very interesting and instructive case and I very much appreciate the privilege of being asked to discuss it. It would appear from the protocol and the autopsy that this infant had a condition which should have been amenable to surgery; it can be profitable to try to determine where mistakes were made, if there were any. I hope that this discussion will be accepted as admittedly dishonest foresight in retrospect.

Unfortunately, it was difficult to obtain very much detail about the early history of this infant. All we know is that the baby was born jaundiced, and was immediately treated for sepsis and bladder infection. It must have recovered swiftly from the sepsis as it was discharged on the thirteenth day, still jaundiced. There is no evidence of whether the jaundice was investigated or not. Three months later the infant was readmitted with abdominal pain and a generalized convulsion. It was explored and found to have biliary atresia. I am not clear whether the exploration was for the jaundice or done as an emergency because of the abdominal pain and the convulsion.

Thus far, the story brings out the point that neonatal jaundice which does not fade rapidly must be watched carefully and investigated. Dr. LoPresti has discussed the tests which are of use and their significance. I wish only to emphasize that a jaundiced infant with acholic stools is seriously ill, and does not have physiological jaundice. Acholic stools are not diagnostic of biliary atresia as they also occur in neonatal hepatitis, and when the common bile duct is plugged with mucus or inspissated bile. It should be possible to establish whether surgery is indicated by the time the infant is between 4 and 6 weeks old. It is important to establish this as early as possible because complete biliary atresia, though compatible with life for some months or even years, damages the liver progressively. It should be borne in mind that every day the obstruction persists, more liver damage occurs. The liver has remarkable powers of regeneration, and much of the liver tissue may be destroyed or removed without danger to life. Nevertheless, several of the reported cases of successful surgical relief of neonatal biliary obstruction have died at a later date of liver failure.

There should not be too much difficulty in establishing a diagnosis of obstructive jaundice if the following points are borne in mind:

1) There will be no bile in the stools or the duodenal secretions;
2) There will be no urobilinogen in the urine;
3) The bilirubin level will be high and show a tendency to steady rise with no drops;
4) The flocculation tests will almost certainly be negative.

There is only one disease that is likely to cause confusion, and that is

neonatal hepatitis. I am not qualified to discuss this condition, but I understand that it is thought to be a viral hepatitis and often no bile is excreted into the intestine during the acute phase. Consequently, it can easily be confused with a true obstructive jaundice. Gross states that it will seldom be confused with those conditions in which surgery is indicated because the cephalin flocculation tests and the bromsulphthalein retention tests are abnormal and the prothrombin time is prolonged. In the cases that I have seen, these points are not certain methods of differentiating, and in the present case by the time the infant was admitted to this hospital, the prothrombin time was markedly prolonged. Needle biopsies of the liver have been advocated but these have two disadvantages. In the first place this condition is, I am led to believe, quite difficult to diagnose from a microscopic section and the pathologist may be reluctant to state definitely that the material is incompatible with a diagnosis of atresia. In the second place a needle biopsy from the liver of an infant with severe jaundice and a prolonged prothrombin time can cause serious intraperitoneal hemorrhage. It is stated that about 60 per cent of infants with neonatal hepatitis will recover spontaneously and surgery should obviously be avoided if possible. However, if infants with obstructive jaundice are to be explored at a time when there is a reasonable prospect of establishing drainage into the intestine with success, the risk must be taken that a certain number will be explored unnecessarily.

There is also one cause of obstruction that may be amenable to medical treatment and that is blockage of the common duct with mucus or inspissated bile. Gellis says that this condition only occurs in cases where there was blood group incompatibility between the mother and the fetus. Gross does not agree with this statement, and in my experience of one case this factor was not involved. Gross reports that Patterson has had some success with the following regime. A duodenal tube is passed and 5 cc. of Decholin® is given intravenously. The duodenal juice is collected for two hours and tested for bile. This is repeated every 2 or 3 days for 2 to 3 weeks. At the same time 250 mgms of Ketochol® (a desiccated bile salt preparation) is given with every feeding. The object is to force the plug out of the common duct with these cholagogues. A positive test for bile from the duodenal juice would be significant evidence of relief of obstruction.

To return to the discussion of this case, at the original exploration the gall bladder and cystic duct were rudimentary and the distal portion of the common bile duct was atretic. Bile was aspirated from the proximal end of the common duct. Since no "T" tube of small enough size was available, a polyethylene tube was tied into the proximal end of the duct and brought out through a stab wound. The abdomen was closed. No bile drained, and three months later the infant was transferred to another hospital. The tube

fell out at this time and the biliary fistula closed. I cannot believe that this is quite correct as there is no mention that bile ever drained, and so the infant never did have a biliary fistula. If it did have one, it seems that some attempt should have been made earlier to transplant such a fistula into the intestine. At the second hospital, surgical exploration was considered, but not undertaken, again because of a lack of a "T" tube of small enough size. I am at a loss to understand this explanation. It is a recognized procedure to use a "T" tube as a splint for an anastomosis when reconstructing a severed bile duct in an adult, bringing the side arm out through a separate opening proximal to the line of anastomosis whenever possible. This is not the case in infants, chiefly owing to the small size of the ducts. The usual technique in infants with atresia is to anastomose the gall bladder, if present, or otherwise the proximal end of the common duct to a convenient piece of intestine, the duodenum or jejunum for preference, forming the anastomosis over a small rubber or polyethylene tube which is allowed to pass out spontaneously by way of the bowel. Though a two layer anastomosis is considered ideal, it is not always possible to get more than one layer in. I do not quite understand why this was not attempted at the first operation rather than bringing the tube to the outside.

When the infant was admitted here, the tests confirmed the complete obstructive jaundice, and fit into the pattern that Dr. LoPresti has explained. The infant was explored surgically in the hope of finding a condition that could still be corrected. The description of the operation reveals the difficulties encountered. The rudimentary gall bladder contained no bile. The cystic duct was transected, and found to have no lumen. The gall bladder was removed, and the common duct explored by cutting across it from below upwards in a series of sections. It was found to be a solid cord up to the *porta hepatis*. At this point, further attempts were abandoned, and the abdomen was closed without drainage. One week later the infant was reexplored because it had manifested signs of intestinal obstruction. The obstruction was found to be due to adhesions between the terminal ileum and the operative site around the *porta hepatis*. This was relieved; the hole in the ileum which became apparent during this procedure was repaired, and the abdomen closed. I think that this was a limited procedure in a very sick baby, and that no effort was made to explore further once the obstruction was found and relieved. After this, the subsequent course showed that the operation was successful in relieving the obstruction, but the jaundice remained, and the infant died three weeks later.

The autopsy findings were most surprising and fascinating. After seeing the autopsy and hearing the story, I was convinced that this was a pseudocyst and not a true cyst. The fact that Dr. Guin has found smooth muscle in the wall is most upsetting. I cannot account for it in any way unless it is.

as it were, an artefact. A pseudocyst is really nothing more than an extravasation of, in this case, bile. This extravasation, instead of flowing freely all over the peritoneal cavity becomes walled off in a circumscribed area. The wall of a pseudocyst consists of fibrous tissue and whatever structure is adjacent. When this cyst was dissected out, part of the wall was so intimately associated with the duodenum that it was impossible to separate the two. It could be that the smooth muscle comes from such a structure which has been incorporated in the wall by the accident of proximity, rather than being an essential primary constituent of it. The only way that I can explain the findings is this: When the infant was explored here for the first time, and the common duct was cut at the *porta hepatis* in the search for a patent duct, at this time the duct was actually patent, at least microscopically; this lumen was blocked by inspissated bile so that the presence of a lumen was not apparent; post-operatively, this plug became dislodged, and bile extravasated; it became locally walled off, and in doing so, caused adhesions with the terminal ileum which led to the subsequent obstruction. This cyst was possibly present at the last operation, but could easily have been overlooked because of the nature of the operation.

Perhaps, the most important lesson that we can learn from this case is one which has a wide application in pediatric surgery. It is this: The first chance is the best chance. At the time of the first exploration, the definitive treatment must be carried out if the best results are going to be obtained. It is rarely possible to institute temporizing procedures while the literature on the subject is consulted. I would even go so far as to say that a surgeon should not consent to explore an infant with a suspected malformation unless he is conversant with the various anomalies that he may discover, and unless he has decided ahead of time what procedure to adopt for each of the possibilities.

In exploring cases of obstructive jaundice, the three conditions which will be encountered most commonly are:

1) Atresia of the bile ducts (about 60 per cent).
2) Neonatal hepatitis (25 per cent).
3) Inspissated bile or mucus blocking the common duct (about 15 per cent).

Biliary atresia may occur at any site in the duct system. In most cases obliteration extends into the ductules in the liver. The minority have the atresia only in the extrahepatic portion of the ducts. It is possible to have patent extrahepatic ducts with intrahepatic atresia. The only cases which are amenable to surgical treatment are those where the atresia is in the extrahepatic duct system, really somewhere in the common duct. These may or may not have a gallbladder. If they do have a gallbladder, it is not

certain that the cystic duct is patent. If there is a gallbladder and it communicates with a patent proximal end of the common duct, the procedure of choice is to anastomose it to either the duodunum or the jejunum. If there is only a proximal end to the common duct, this should be used for the anastomosis, and the technical difficulties of the operation are increased.

If the condition of neonatal hepatitis is encountered, there is nothing to be done surgically, though the pathology department seems to expect its *quid pro quo* in the form of a biopsy.

If the duct is blocked by inspissated bile, this can usually be washed out by inserting a needle into the apex of the gall bladder and forcing fluid in under pressure at the same time that the duct is milked manually towards the duodenum. The common duct has been opened and probed in these cases but it is quite a trick to perform, and is usually unnecessary.

It is relatively easy to know what to do when the diagnosis has been made, but it can be very difficult to decide at operation just what the condition really is. It may require very careful dissection. The transverse incision has two great advantages over the long paramedian. The first is that it requires the minimum of retraction for the maximum of exposure. This leads to the second advantage, (particularly if combined with a selfretaining retractor) that is, that the depth of anaesthesia can be very much lighter during the major part of the procedure. Thus, the length of time taken during the operation is less important.

After the abdomen is opened the gall bladder should be looked for, and if it is found, a needle inserted into it with a purse string around the puncture site. Aspiration will tell whether the gall bladder contains bile or not. It is important to remember that all the body fluids of a severely jaundiced infant are greenish yellow, but that the bile, if present, will be dark and thick. After aspirating the contents of the gall bladder, Diodrast®, or a similar radiopaque fluid should be run in to try to fill the ducts, and a radiograph taken. It is advisable to have the x-ray film under the infant before the operation starts, and then it is a simple matter to swing a portable tube over the operative field and take an x-ray. The dye may be seen to flow readily into the duodenum. In this case there is either atresia of the intrahepatic ducts, or hepatitis. It is sometimes possible to distinguish between these two as well, because in the cases of hepatitis the hepatic ducts themselves will be outlined, but if there is intrahepatic atresia, they will not. In either case there is nothing to be done surgically. I suppose that one could consider Longmire's operation, but this has not been successfully performed for this condition to the best of my knowledge, and there are theoretical reasons why it should not work.

If the dye does not flow into the duodenum, either a plug of mucus or bile must be holding it up, or there must be a distal atresia. The common duct

must be dissected out, and whichever of these conditions is found can be corrected. In doing this, the exposure is facilitated if the mesenteric folds attaching the hepatic flexure over the duodenum are first divided. This enables the large bowel to be packed out of the way much more successfully.

If there is no gall bladder, it is just a question of dissecting out the common duct itself, and the chances are very strongly against the case being one of hepatitis with congenital absence of the gall bladder. Incidentally, in the series reported from the Children's Hospital in Boston, only one "operable" case did not have a gall bladder out of a total of 142 cases of atresia, though in ten cases the gall bladder did not connect with the common duct which was atretic above the cystic duct, but still outside the *porta hepatis*. It is not easy to dissect out the common duct in these infants. Gross reports three cases where no evidence of any extrahepatic ducts was found. The babies recovered and subsequently, their jaundice cleared, and their stools became normal. He assumed that these infants had very small ducts which became blocked with bile, and cleared themselves. It does illustrate that even in the best hands, normal ducts can be overlooked. I think that the operative cholangiogram is a most useful adjunct and can save the surgeon a lot of headaches.

There are three other causes of jaundice which should be remembered as possibilities, though they are not usually found in neonatal cases:

1) Extrabiliary obstruction. We had such a case in the hospital here recently where the obstructive jaundice was due to kinking of the common bile duct by a neuroblastoma which was behind the foramen of Winslow. Such obstruction also may be due to an enlarged gland at the cystic duct.

2) Choledochal Cysts. Five per cent only are under 6 months of age, and they are typically accompanied by a triad of symptoms; pain, intermittent jaundice, and an abdominal mass.

3) Cholecystitis. Stones are rare as a cause in children, but jaundice is more common than in adults with this condition.

If this case is one of a pseudocyst, I understand that there is only one other recorded in the literature. Dr. Gilbert called my attention to a report of Smith in *Pediatrics 1953*. In this case the cyst followed trauma to the common bile duct during a Rammstedt operation. It was successfully treated by ligating the common duct proximal to its entrance to the cyst, but distal to the cystic duct, and anastomosing the gall bladder to the stomach.

A STUDY OF HEREDITARY DEFECTS OCCURRING IN A RACIAL ISOLATE RESIDING IN SOUTHERN MARYLAND

Special Report

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A group of 4,000 to 5,000 related persons of Caucasian, Negro and American Indian ancestry resides in southern Maryland and the District of Columbia. This group was separated from the white community sometime before 1741, and they did not consider themselves Negroes. As a result, they maintained their racial integrity by in-marriage within fourteen families[1]. After several centuries of in-marriages many genetically recessive traits became manifest and many genetically dominant traits became concentrated in certain lines of the clan. Many of these traits are of special interest to the pediatrician as well as the geneticist.

The genetic aspects of these people were first studied by Hursey, et al.[2], who described dentinogenesis imperfecta in patients seen at Children's Hospital, and by the senior author, who observed the same condition during a survey of school children in Maryland. These people are now being studied by the National Institutes of Health. This group offers special advantages for studies in the fields of genetics, medicine, dentistry and sociology: many matings, rare in human material, occur here; the people live for the most part in one geographic location; there are written records on births, deaths, and marriages for several hundred years which have been made available to this study; there are enough living members so that any statistical estimation can be based on data obtained from patients actually examined, provided the relationship of the living members to each other is known; and the group is large enough to approach the size desired in a population study.

The purpose of this paper is to present a short description of some of the genetically determined conditions that occur in these people. Thus far, only a portion of the population has been studied.

DENTINOGENESIS IMPERFECTA

Dentinogenesis imperfecta, also known as opalescent dentin, occurs as a separate clinical entity, and may sometimes occur as a manifestation of the

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osteogenesis imperfecta syndrome[3]. The teeth are usually amber brown in color with an opalescent hue. The enamel readily fractures from the dentin, especially on surfaces in occlusion. The teeth usually have obliterated pulp chambers. This trait occurs in the general population about once among 6,000 persons.

In the present group over 78 cases of this condition have been described. It is transmitted as an autosomal dominant trait with complete penetrance. It is always transmitted by a person with the defect. We have found marriages where both partners have this condition. In one such example, the mother has had five miscarriages and two viable births. It is possible that some of these miscarriages may be due to a lethal effect of the homozygous condition of these genes. A close study is being made of these cases and will be reported at a later date.

There are wide variations in the clinical appearance of this trait from case to case. In most instances, the pulp chambers of the teeth are obliterated. Some cases show pulp chambers of normal size. A few individuals have "shell" teeth containing very large pulp chambers surrounded by a thin layer of dentin. The cases of "shell" teeth do not represent the homozygous condition of the trait.

LOP EARS

Hereditary lop ears, usually transmitted as an autosomal dominant trait[4], are characterized by a lack of cartilage in the antihelix. The frequency of this trait in the general population is not known.

In the present study we have found at least 18 individuals with this defect. Some individuals show a folding of the superior portion of the major helix. In others, there is a definite notch in the helix. The adults with this trait also show a juvenile type of external auditory canal which runs sharply anteriorly then posteriorly on its way to the tympanic membrane. One individual, who could be homozygous for this trait, had only rudimentary external ears. The defect appears to be transmitted as an autosomal dominant trait in this group.

ALBINISM

Albinism is frequently found in inbred populations, and it is a fairly common recessive trait in both plants and animals. The frequency of this anomaly in the population is estimated at 1:10,000–20,000[5].

In the group under study, we have found 15 cases of albinism to date. The individuals with this condition have colorless hair and pink-white skin. There is some gray pigmentation present in the irises of their eyes. This condition is transmitted as a recessive trait in this group.

ALBERS-SCHÖNBERG DISEASE

Albers-Schönberg osteopetrosis has been reported to occur as a recessive trait, although some forms of osteopetrosis have been shown to occur over three generations[6]. The frequency of this trait in the general population is not known.

In the present group only one sibship has been found with affected individuals. These cases have been previously reported by Kelly and Lawlah[7]. Four sibs were affected and six unaffected in this sibship. Besides the skeletal involvement, there was also involvement of the seventh and eighth cranial nerves in these cases, manifested by facial paralysis or weakness and loss of hearing. In one case acromegaly developed later. The condition is transmitted as a recessive trait in this group.

POLYCYSTIC DISEASE OF THE KIDNEYS

Polycystic disease of the kidneys has been described as two distinct varieties, congenital cystic kidney and cystic disease of the kidney in adults. The adult type develops at about 40 years of age, and is often accompanied by hypertension. The congenital type, causing death shortly after birth, is said to be recessive, while the adult form shows a dominant inheritance[8].

In our group, this disease has been traced through four generations of the family. The mode of inheritance appears to be a dominant one. The affected individuals died between 38 and 48 years of age with accompanying hypertension. One case, seen in Children's Hospital, occurred in an albino. There is some question concerning the separation of cystic kidneys into two varieties. Cases do occur that do not seem to fit into these types. In our study two cases appear in children at early ages, but the adult form seems to predominate.

FIBROCYSTIC DISEASE OF THE PANCREAS

The incidence of fibrocystic disease of the pancreas in the general population probably is somewhere between 1:1000–10,000 births. There is some question about the mode of inheritance of the disease, but most work tends to show that it is due to a recessive gene. It was suggested that some spheterozygotes secrete increased amounts of sodium chloride in sweat[9].

In this group fibrocystic disease of the pancreas occurs either as a recessive or as a sporadic trait. We have not accumulated enough evidence to indicate the prevalance of this trait in the group. One case, which was autopsied at Children's Hospital, showed mucoviscidosis and abnormalities of parotid saliva salt content. Analysis of the salt content of saliva and sweat of the individuals in this sibship and the parents is being done to detect carriers of this gene.

SICKLE-CELL DISEASE

Direct estimates of the frequency of sickle-cell disease are not available. However, it is estimated that 9 per cent of the American Negroes show sickle-cell trait, and from this figure it is calculated that sickle-cell disease should have a frequency of 2.2 per 1,000 at birth[10].

In our study, several sibships have been found showing both sickle-cell disease and sickle-cell trait. Both parents in these instances were heterozygous for the sickle-cell gene. Electrophoretic studies of the hemoglobin of these cases are incomplete, but those tested showed S type hemoglobin.

COMBINATIONS OF TRAITS AND ANOMALIES

Some individuals in this study have shown combinations of several traits. Four patients have lop ears and dentinogenesis imperfecta. An albino has polycystic kidneys. A three year old boy with dentinogenesis imperfecta died with Eisenmenger's complex. A mongoloid child exhibited the ear defect. One child has lop ears, dentinogenesis imperfecta, hypertelorism, deaf-mutism, and mental deficiency. In most of these instances we have been able to show the independent inheritance of some of these conditions from different lines of affected parents. The occurrence of these conditions in one individual is most likely due to a chance combination of these traits and does not represent a syndrome.

REPRODUCTIVE CAPACITY

The reproductive capacity of these people as a group does not seem to be impaired. It is estimated that the average woman had 5.7 offspring over the reproductive years 1900 to 1950. This estimate was obtained by considering only sibships in which all women are now over 50 years of age, determining the number of women originally in that generation, provided they lived more than one day, and then determining the number of offspring these women had in the following generation.

OTHER CONDITIONS OF INTEREST AND FUTURE STUDIES

There are several other conditions which seem to be exceptionally prevalent in this group or which warrant attention because of the unusual social environment in which the people live. A study of mental illness in the group is being made, since a preliminary survey suggests that there is a large number of cases of schizophrenia and mental deficiency in certain family lines. Evaluation of intrinsic and extrinsic factors in these conditions awaits detailed studies. There is some indication that cyanotic and acyanotic congenital heart disease may be somewhat more common in this group than expected. One sibship has five cases of cyanotic heart disease, another three, and several two. A blood typing program and a study of pregnancy

wastage related to A and O type blood groups is in progress. A study of diabetics from this group is planned. Over 30 cases of dyspnea which have been diagnosed as asthma have been found. One individual is an achondroplastic dwarf. Information on this particular trait, as it occurs in this group, is not complete.

This study is planned in three phases:

1. A census and genealogy of the group is being made, and a medical history is being obtained from each member.

2. Dental and medical field examinations will be started in the near future.

3. Individuals with certain conditions will be selected for detailed hospital studies.

It is contemplated that the entire study will be completed in five years. Because of the unusual sociological problem inherent in a study of this type, we must protect the privacy of the individuals, the families, and the group as a whole. We have established an excellent rapport with the group. The final success of this study will depend upon the cooperation of the local practitioners, the hospitals, and the community health agencies, as well as the people themselves.

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TETRALOGY OF FALLOT

Review of Literature

George William Ware, M.D.

Tetralogy of Fallot is a congenital cyanotic cardiac condition consisting of the following defects: pulmonic stenosis, right ventricular hypertrophy, interventricular septal defect and over-riding of the aorta. The pulmonic stenosis may occur at the level of the pulmonic valve, or in the right ventricle itself, so-called infundibular stenosis.

The condition is common. Blalock has estimated that 70 per cent of children over 2 years of age who are cyanotic because of congenital heart disease have the tetralogy of Fallot.

History[1-4]

Sandifort in 1783 was the first to describe the various anomalies in this condition. Hope and Peacock reported cases in 1839 and 1866 respectively, Hope's patient having been diagnosed during life. Fallot in 1888 reviewed the literature and added 3 cases of his own. Because of the completeness of his work and his stress on clinical diagnosis, the condition is commonly called tetralogy of Fallot.

Modern therapy began with the combined efforts of Taussig and Blalock of John Hopkins Hospital. Taussig observed that cyanosis appeared in this condition when the ductus arteriosus closed. She interpreted this to mean that cyanosis was the result of inadequate pulmonary blood flow. She suggested to Blalock that these patients would be benefited if he could devise a means of increasing pulmonary blood flow. Blalock's experiments bore fruit when he devised a systemic pulmonary vascular shunt, usually anastomosing the subclavian artery to the pulmonary artery. The first patient was operated upon on November 2, 1944.

Embryology and Pathology[1, 3, 5-8]

The embryonic heart is a tubular structure consisting of a common atrium and ventricle. The atrium is originally inferior in position to the ventricle. The sinus venosus connects with the atrium. The arterial counterpart is the conus arteriosus and connects the ventricle to the truncus arteriosus.

The heart grows rapidly so that it projects anteriorly and ventrally, forming a U-shaped loop. This phase brings the ventricle to a position inferior to the atrium. This twisting growth also brings the truncus arteriosus into a position adjacent to the common ventricle. Fusion occurs with the portion of the common ventricle which later becomes the right

ventricle. In postnatal life the truncus persists as a muscular band on the dorsal wall of the interior of the right ventricle and is then called the crista supraventricularis.

As the heart is projecting forward, ridges of proliferating endothelium appear in the common truncus-conus channel. These ridges grow downward in a clockwise spiral manner towards the developing interventricular septum. As they meet and fuse, they transform the common channel into future aorta and pulmonary artery. The clockwise, spiral growth connects aorta with left ventricle and pulmonary artery with right ventricle.

In tetralogy of Fallot, the origin of the truncus-conus ridges is misplaced, and hence an irregular spiral is formed. This accounts for overriding of the aorta. The normal fusion of these ridges in their lower portions aids in the formation of the interventricular septum. Because of the misplaced origin, the fusion does not occur at the necessary level to take part in the interventricular septum. Hence, a high interventricular septal defect occurs. Infundibular stenosis results from maldevelopment of the crista supraventricularis. Normally, this is a muscular ridge on the posterior wall of the right ventricle, extending from pulmonary valve down to tricuspid valve. Dry has pointed out that in tetralogy, the aorta occupies a position posterior to the crista supraventricularis. In his opinion, the aorta crowds the crista into an anterior position, thus creating infundibular stenosis. Since the crista almost touches the anterior wall of right ventricle, in effect, there is created a separate chamber in the right ventricle.

It should be remembered that in 20 to 25 per cent of cases, the aorta will descend on the right.

The exact nature of stenosis of the outflow tract of the right ventricle will vary. Johns has reviewed 95 autopsy cases from Johns Hopkins. The vast majority had undergone surgery. Pulmonary atresia was noted in 22 cases; infundibular stenosis occurred in 49 cases; valvular stenosis occurred in 10 cases; combination of valvular and infundibular stenosis was present in an additional 14 cases. Bailey, in an operative series of 95 patients, has recorded 64 instances of infundibular stenosis, 20 cases of valvular stenosis, 3 patients with atresia of pulmonary artery. The remaining 8 cases had combined valvular and infundibular stenosis.

Signs and Symptoms[4-7, 9-11]

Cyanosis. This is usually noted at birth. If the ductus arteriosus remains patent, cyanosis is not noted until obliteration occurs. The degree of cyanosis varies. It is usually progressive and is increased on exertion. The exercise tolerance is directly correlated with the degree of cyanosis.

Dyspnea. This is a common complaint due to low arterial oxygen saturation.

Syncope. This is common in the more severe forms. Its occurrence may be a warning of an impending cerebral vascular thrombosis.

Appetite, weight gain. These are poor. The patient frequently finds that dyspnea and syncope are more common after heavy meals.

Physical stature. Patients are usually frail. Mentally they are normal regardless of the degree of cyanosis.

Clubbing of fingers and toes. This is quite common.

Heart. A systolic murmur is heard over the precordium or to the left of the sternum. The murmur is usually loud and accompanied by a thrill. Systolic blood pressure is commonly low.

Squatting. An interesting phenomenon observed in the vast majority of patients is the practice of squatting on their haunches following physical exercise or standing. Recently Lurie has published interesting data to explain this habit. The upright position decreases venous return to the heart and in patients with tetralogy of Fallot, increases the arterial desaturation. Squatting improves venous return by compressing veins of abdomen and legs and also by bringing these channels closer to the heart. Arterial oxygen saturation is improved with the increased venous return.

Laboratory Data[12-15]

Red blood cells. The common range is between 6 and 7 million per cubic millimeter. Cell counts up to 10 million have been reported.

Hemoglobin. This may attain levels of 160 per cent.

Hematocrit reading. This may be over 60 per cent.

Oxygen arterial saturation. This is reduced at rest and falls still further with exercise.

Bleeding studies. With the performance of surgery in this condition, it became apparent that certain cases bled severely in the early post-operative period. This complication only occurred in the adolescent and adult patients. Hartman studied patients with congenital cyanotic heart disease in this age group. He found that such patients had a high hematocrit, thrombocytopenia, low plasma fibrinogen and very poor clot retraction. Phlebotomy will reduce red cells and proportionately increase blood fibrinogen.

Roentgenography[5, 9, 11, 16-18]

On the routine chest film, the heart appears normal. It may be described as "boot-shaped" when hypertrophy of the right ventricle elevates its apex. Pulmonary vascular markings are decreased and the lung fields are clear.

On fluoroscopy there is noted diminished pulsation of the hilar vascular structures. There is no fullness in the area of the pulmonary conus. In 25

per cent of cases, barium swallow shows the esophagus to be indented on the right by the aorta, indicating a descending right aortic arch.

Angiocardiography is of distinct help. After injection, the dye will be seen to fill simultaneously the aorta and pulmonary artery. This shows the presence of ventricular septal defect and over-riding of the aorta. The surgeon will be aided by this study since he can ascertain presence and size of pulmonary arteries.

Cardiac Catheterization[9, 19]

If the exploring catheter can be passed from right ventricle to left, the septal defect is proved. If the catheter can be passed from right ventricle to aorta, over-riding of aorta is demonstrated.

One can not always introduce the catheter into the pulmonary artery during the catheterization, but, if so, valuable pressure tracings can be obtained. Due to pulmonic stenosis, right ventricular pressure is increased while pulmonary artery pressure is decreased. On withdrawing the catheter from the pulmonary artery to the right ventricle, a sharp rise in pressure is obtained at the level of the pulmonic valve when valvular obstruction is present. If the rise does not occur until lower in the ventricle, infundibular stenosis is present.

Electrocardiography

Right axis deviation due to right ventricular hypertrophy is the rule.

Differential Diagnosis[4, 5, 15, 20]

Eisenmenger's Complex. (Ventricular septal defect, over-riding of aorta, right ventricular hypertrophy.)

These patients are usually less cyanotic. There is no pulmonary stenosis, hence pulmonary arterial pressure is high and may equal systemic arterial pressure. The Bing test is valuable. In patients with tetralogy of Fallot there is a fall in oxygen consumption per liter of ventilation with exercise. In patients with Eisenmenger's complex (and in normal patients) there is an increase in oxygen consumption per liter of ventilation with exercise.

Pulmonic Stenosis Associated with Atrial Septal Defect. During cardiac catheterization one is able to pass the catheter into the left atrium from the right atrium. The aorta can not be entered from the right ventricle. Angiocardiography will demonstrate the atrial septal defect.

Tricuspid atresia. Since there is hypoplasia of the right ventricle, the electrocardiogram will show left axis deviation. Angiocardiograms will show trapping of the dye in right atrium and a diminutive right ventricle. On

plain chest film the heart border can not be visualized to the right of vertebral column.

Persistent truncus arteriosus. Routine chest films will show left and right ventricular enlargement. EKG will usually show mild right axis deviation. Angiocardiogram will show origin of pulmonary arteries from the truncus arteriosus.

Surgery

A. *Extracardiac Procedures*

1. *Blalock-Taussig Operation*[1, 21, 22]

This operation consists of an anastomosis between the subclavian and pulmonary arteries; such an anastomosis provides extra pulmonary vascular flow. The preferred age for surgery is 5 years or older. In younger patients Blalock prefers to use the subclavian vessel which branches from the innominate artery. Since in the majority of instances a left descending aorta is present, this operation involves a right thoracotomy. In patients over 12 years of age Blalock prefers to use the subclavian vessel which branches directly from the aorta. This latter vessel is the one preferred by most surgeons regardless of the age of the patient.

2. *Potts Procedure*[23-26]

This operation involves a direct anastomosis between aorta and pulmonary artery, done for the same reason as the Blalock anastomosis. The operation is especially applicable in young infants in whom the subclavian vessels are too small for an adequate anastomosis. A major drawback of the operation is the danger of congestive heart failure if the anastomosis is too long or large.

3. *Complications of Extracardiac Surgery*[12, 15, 24-27]

Cardiac failure. Increase in heart size occurs in patients after both the Blalock and Potts procedure. Cardiac failure is uncommon. Bahnson has reported that 3 per cent of the first 500 patients operated at Johns Hopkins Hospital died of congestive heart failure. Campbell has reported 2 cases of cardiac decompensation following 200 cases of Blalock procedure.

Anastomotic thrombosis. Bahnson has reported five instances in the first 500 cases done at Johns Hopkins Hospital. Potts has reported 1 thrombosis in the first 100 cases performed at his institution.

Cerebral thrombosis. This complication is common if the carotid or innominate artery is used for a Blalock anastomosis. Anoxia during surgery and dehydration are also important factors.

Postoperative hemorrhage. Hartman has reported 18 fatal episodes of hemorrhage in 1,100 Blalock anastomoses. Potts has noted 3 instances in 181 operations.

Bacterial endarteritis. This condition is uncommon. Campbell encountered

it once following 2,000 operations. In a review of 1,000 cases Taussig noted the disease in 18 patients. Onset shortly after surgery was the rule. Four patients succumbed.

4. *Results of Extracardiac Surgery*

Taussig has reviewed 857 cases of tetralogy of Fallot who underwent such surgery. Eighty per cent had good results, 3 per cent had fair results, the remainder were unchanged. The operative mortality for the entire series was 14 per cent.

Campbell has reported 200 cases who underwent extracardiac surgery at Guy's Hospital, London. About 20 patients did not have tetralogy of Fallot. Exploratory thoracotomy only was done in 11 instances. One hundred and thirty-six patients had a good to fair result. No improvement was noted in 6. Twenty-four patients did not survive surgery.

Potts et al. have recently reviewed their first 100 surgical cases. These patients have been followed six to eight years. Sixty-eight patients were considered to have had a good result, 16 patients had a fair result, one patient had a poor result, and another patient's condition was unchanged by surgery. Nine patients died during their hospital stay. Early improvement was noted in an additional 5 who later succumbed.

B. *Intracardiac Procedures*

1. *Direct Attack on Stenotic Pulmonic Valve or Infundibulum*[5, 6, 28-35]

A basic defect of the Blalock procedure is that it does not directly treat any of the congenital defects present. Indeed an additional defect is added, namely, an artificial patent ductus arteriosus. This defect, if it existed alone, would be reason for corrective surgery because of the fear of heart failure and bacterial endarteritis. Another objection is the fear that an anastomosis sufficient for a child may not be sufficient when he has reached adult life.

Attempts have therefore been made to attack directly the stenotic area. The pioneers in this surgery have been Brock in England, and Bailey and Glover in this country. If valvular stenosis is present, it is divided with a special knife passed through the right ventricle. Infundibular stenosis is resected with rongeurs through a similar approach.

Brock has operated 39 tetralogies with pulmonic valvular stenosis. The results were good to excellent in 29, fair in 7. Three patients died. The same surgeon has operated 29 cases of tetralogy with infundibular stenosis. Seven died. An additional 10 cases had combined infundibular and pulmonary stenosis (all of this group lived). The results were good to excellent in 28, fair or poor in 4.

2. *Corrective Procedures*[36-40]

It has long been the dream of the surgeon to develop some device which would enable him to open the heart and attack congenital defects directly.

This dream has been the spur to investigations in the field of heart and lung machines. Such machines are designed to take over oxygenation and circulation of the blood while the heart is excluded from the circulation. Isolated clinical success has been obtained in the treatment of certain congenital defects, e.g., interventricular septal defects. To my knowledge however, they have never been used successfully in a patient suffering from tetralogy of Fallot.

The most notable advance in this field has been made by the University of Minnesota Group in the development of "controlled cross circulation". Such a method makes use of the "azygos flow principle". In brief explanation of this principle, it has been found that with both venae cavae clamped, the blood flow returning to the heart through the intact azygos vein is sufficient to maintain life for long periods of time. When the amount of this azygos flow is measured it is found to be far less than the basal cardiac output, the value usually accepted as the lowest flow compatible with life. Knowledge of a lower volume needed has reduced the need for huge cumbersome heart-lung machines for the circulation and oxygenation of blood.

In directly repairing cardiac defects in children, the Minnesota Group has used a human donor of compatible blood type for the oxygenation and circulation of the patient's blood during cardiac repair. Mechanical movement of blood between patient and donor is accomplished by a rather simple pump. Blood flow during the repair has been maintained at approximately 25 ml per kilogram of body weight per minute. Heart-lung machines are constructed to maintain a flow equal to basal cardiac output: 100–150 cc per kilogram of body weight per minute. At such a flow rate it is obvious that a more complicated machine is needed. Utilizing controlled cross circulation the Minnesota Group has operated on 10 patients with tetralogy of Fallot. The period of open cardiotomy varied from 6 to 21 minutes. Six patients survived surgery. There was no donor mortality.

CONCLUSION

It is thus seen that there are many operative approaches for the surgical treatment of tetralogy of Fallot. It is the author's opinion that in the near future a standardized method of controlled cross-circulation or a feasible heart-lung machine will be available. Such methods will provide the preferred approach for the correction of tetralogy of Fallot. With this basic premise, it would follow that surgery should be deferred until these agents are available. The clinician, faced with a patient who is unable to await the future, should recommend a Blalock or a Potts procedure.

However intriguing direct attack on the valve or infundibulum might seem, it is rendered obsolete by the advent of "controlled cross-circulations". The Brock procedure does not repair the septal defect or correct

over-riding of the aorta. More important the operation requires extensive incision of the pericardium resulting in marked adhesions. Such adhesions render later corrective surgery difficult and hazardous. Indeed fatal rupture of the right ventricle has occurred during "controlled cross circulation" due to these adhesions.

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*Lee, H. F., in Lull & Kimbrough: Clinical Obstetrics, Philadelphia, Lippincott, 1953, pp. 630-632.

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